Towards a noninvasive anatomical and functional diagnostic work-up of patients with suspected coronary artery disease

J.G.J. Groothuis, A.M. Beek, M.R. Meijerink, S.L. Brinckman, M.B.M. Hofman, A.C. van Rossum

Combining multidetector computed tomography and cardiovascular magnetic resonance imaging provides the clinician a strategy to comprehensively evaluate coronary morphology and function noninvasively. In the MARCC trial (Magnetic Resonance and CT in suspected CAD) a new noninvasive diagnostic work-up for patients with suspected coronary artery disease will be developed, involving the sequential use of both imaging techniques. (Neth Heart J 2010;18:270-03.)

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J.G.J. Groothuis

A.C. van Rossum

*Interuniversity Cardiology Institute of the Netherlands, Utrecht, and
Department of Cardiology, Institute for Cardiovascular Research, VU
University Medical Center, Amsterdam, the Netherlands*

A.M. Beek

S.L. Brinckman

*Department of Cardiology, Institute for Cardiovascular Research, VU
University Medical Center, Amsterdam, the Netherlands*

M.R. Meijerink

*Department of Radiology, VU University Medical Center, Amsterdam,
the Netherlands*

M.B.M. Hofman

*Department of Physics and Medical Technology, Institute for
Cardiovascular Research, VU University Medical Center, Amsterdam,
the Netherlands*

Correspondence to: J.G.J. Groothuis

VU University Medical Center, Department of Cardiology, Room 5F003,
PO Box 7053, 1007 MB Amsterdam, the Netherlands
E-mail: j.groothuis@vumc.nl

Whereas the diagnostic evaluation of patients with suspected coronary artery disease (CAD) is part of the daily routine of cardiology practice, the conventional modalities for detection of CAD have major limitations. Even though its prognostic value has been validated extensively, exercise electrocardiography only has a limited diagnostic value for detection of significant CAD, with a reported sensitivity and specificity of 68 and 77%, respectively.¹ Additionally, in a large proportion of patients results are inconclusive. Although single photon emission computed tomography myocardial perfusion imaging (SPECT) is more sensitive for detection of significant CAD, it only has a moderate specificity.² Consequently, this leads to a considerable number of unnecessary referrals for invasive coronary angiography. Furthermore, a combined SPECT stress and rest protocol involves a significant radiation burden (10-20 mSv), and requires two separate scanning sessions.

Recently multidetector computed tomography coronary angiography (CTCA) has been developed and is increasingly used in clinical practice. CTCA is the first technique that enables the clinician to accurately visualise the coronary arteries and their atherosclerotic plaque non-invasively. In contrast to conventional functional techniques, CTCA detects CAD at a much earlier stage, when it has not yet become haemodynamically relevant. Since acute myocardial infarctions often result from rupture of only mildly stenotic atherosclerotic plaques, detection of these plaques has significant prognostic relevance.³ Several studies have investigated the diagnostic performance of CTCA for the detection of significant CAD.⁴ In the majority of studies the negative predictive value of CTCA for detection of CAD was excellent. Therefore, this technique is particularly valuable for ruling out CAD in patients at low risk of having CAD.⁵ Accordingly, recent guidelines included CTCA for patients with low or intermediate

probability CAD.^{6,7} Although its negative predictive value is high, the positive predictive value is quite low due to beam hardening artifacts of calcified atherosclerotic plaques, which cause overestimation of stenosis severity. Furthermore, several studies have shown that CTCA cannot accurately predict the haemodynamic relevance of CAD.^{8,9} Thus, when severe CAD is detected by CTCA, additional noninvasive functional testing is needed to assess the haemodynamic significance of disease, before referral for invasive coronary angiography.

Cardiovascular magnetic resonance (CMR) imaging has evolved from an effective research tool into a clinically established imaging modality for the evaluation of ischaemic heart disease.¹⁰ CMR provides anatomical and functional information in acquired and congenital heart disease and is considered the gold standard for quantification of ventricular volumes, function and mass. Delayed contrast-enhanced CMR is an accurate and robust method to depict and quantify regional myocardial scarring, and can be used in the diagnosis and management of heart disease of ischaemic as well as nonischaemic origin.^{11,12} Adenosine stress and rest first pass magnetic resonance myocardial perfusion

imaging (MRMPI) can accurately detect myocardial ischaemia. It has been validated against positron emission tomography,¹³ fractional flow reserve¹⁴ and intracoronary flow measurements.¹⁵ Recently, it has been shown that MRMPI has at least a similar diagnostic performance for detection of significant CAD to SPECT.¹⁶ Furthermore, several studies have shown a similar prognostic value of MRMPI in comparison with SPECT.^{17,18} MRMPI has several advantages in comparison with SPECT: it can assess myocardial perfusion, ventricular function and myocardial viability in one single scan session and it does not involve any ionising radiation. Therefore, MRMPI may be the ideal additional functional imaging technique to CTCA in the diagnostic work-up of patients with suspected CAD. CTCA and MRMPI images of a patient with intermediate probability CAD are shown in figure 1.

To develop a new noninvasive diagnostic algorithm involving the sequential use of both imaging techniques we have started the MARCC trial (Magnetic Resonance and CT in suspected CAD). In this ongoing trial a new noninvasive diagnostic work-up for patients with suspected CAD will be developed using CT coronary calcium scoring, CTCA and

Figure 1. Images of a 58-year-old man with atypical chest pain. CTCA image showing noncalcified atherosclerotic plaque in the proximal left coronary artery causing >50% diameter stenosis (A, arrowheads). Adenosine stress (B-D) and rest (E-G) magnetic resonance myocardial perfusion images on a mid ventricular short axis level at three time points during first pass of a contrast bolus through right and left ventricle and perfusion of the myocardium. During adenosine stress a perfusion defect is visible in the anterior myocardial wall (B-D, arrowheads) that is not present at rest (E-G).

CMR. A total of 220 patients with chest pain and low to intermediate probability of CAD according to the combined Diamond/Forrester and CASS scale will be included.¹⁹ These patients undergo CT coronary calcium scoring, 64-slice CTCA (Siemens Sensation 64) and CMR imaging (involving assessment of left ventricular function, adenosine stress and rest myocardial perfusion and delayed contrast enhancement). These noninvasive parameters will be compared with invasive coronary angiography and fractional flow reserve measurements. All patients will be followed up after one year by telephone interview for clinical status, an interval diagnosis of significant CAD on invasive coronary angiography and major adverse cardiovascular events. Primary endpoints are the diagnostic performance of these imaging modalities for detection of significant CAD on invasive coronary angiography and one-year clinical outcome. From these data a new diagnostic algorithm (decision-tree model) will be developed involving the sequential use of these imaging modalities. Finally, the cost-effectiveness of the proposed algorithm will be compared with conventional strategies involving exercise electrocardiography and SPECT.

Recently, we reported on the complementary role of CTCA and MRMPI in the first 154 patients included in the MARCC trial.²⁰ Both CTCA and MRMPI were performed successfully in 145 of 154 patients (94.2%), confirming the feasibility of the combined use of these modalities. In 90.5% (57/63; 95% CI 82.6 to 95.0) of patients without any CAD on CTCA, normal myocardial perfusion on MRMPI was found. Of patients with nonobstructive CAD on CTCA, 83.3% (25/30; 95% CI 69.5 to 91.6) had normal myocardial perfusion on MRMPI. In patients with obstructive CAD on CTCA (>50% diameter stenosis), only 42.3% (22/52; 95% CI: 29.5 to 56%) had myocardial ischaemia on MRMPI. Thus, although CTCA could reliably rule out significant CAD, detection of myocardial ischaemia was limited. These results show the complementary role of CTCA and MRMPI in the evaluation of patients with suspected CAD. Combining both imaging modalities enables the clinician to comprehensively evaluate coronary morphology and function noninvasively. Since imaging modalities are applied in a sequential way in clinical practice, the MARCC trial aims at finding the most optimal diagnostic algorithm, involving the sequential use of CT calcium scoring, CTCA and CMR.

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